REMARKS

Because the prior amendment submitted on October 20, 2005 was not entered, applicants resubmit their prior amendments and expand the prior arguments to address the rejections presented in the prior Office Action of April 20, 2005, and the Advisory Action of November 9, 2005. Claims 5-8, 10-22, 25-39, 41, 43, 45-70, and 72-91, as amended appear in this application for Examiner's review and consideration. Claims 5, 8, 10, 13, 16, 22, 32, 34, 36, 54-55, 57, 68, 74-76, 82, 85, and 87-91 have been amended to clarify the subject matter of the claims. No new matter has been added to these claims.

Claims 22, 74, 75, and 76 have been amended to correct typographical errors. Claim 22 has been amended to delete one of the powder x-ray diffraction ("PXRD") peaks at "10.5" degrees two-theta, as it has been recited twice. In claim 74, the symbol "+" has been replaced with the symbol "±". In claims 74-76, the phrase "two-theta" has been added to identify the units of measurement for the PXRD diffraction pattern. No new matter has been added to claims 22, 74, 75, or 76.

Claims 89-91 have been amended to recite pharmaceutical compositions comprising ondansetron hydrochloride. These amendments find support on page 14, lines 10-16 of the specification.

Applicants' appreciate the courtesies extended to their representative, Craig L. Puckett, Reg. No. 43,023, during the interview with Examiner Taylor Victor Oh conducted on October 19, 2005. The substance of the interview and the reasons presented at the interview as warranting favorable action are included in the comments below.

Claims 89-91 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. Applicants respectfully traverse.

The enablement requirement of 35 U.S.C. § 112, first paragraph is fulfilled when the patent discloses enough information about the claimed invention to enable one skilled in the art to make and use it without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

The Office asserts that claims 89-91 "are directed to a pharmaceutical composition comprising the polymorphic various forms of ondansetron hydrochloride" Office Action dated July 28, 2004, p. 3. The Office maintains that claims 89-91 are not enabled, because "the skilled artisan in the art is unable to

determine which polymorphic form of ondansetron hydrochloride is suitable for the pharmaceutical composition with respect to the pharmaceutical bioavailability". Office Action dated July 28, 2004, p. 4.

Initially, the rejection in the Office Action of April 20, 2005 or as reiterated in the Advisory Action of November 9, 2005 is insufficient to comply with 37 C.F.R. § 1.104(2) where the "the reasons for any adverse action or any objection or requirement will be stated in an Office Action and such information or reference will be given as may be useful in aiding the applicant ... to judge the propriety of continuing the prosecution." The Office Action merely maintains the prior rejection, "due to applicants' failure to modify the claims in the amendment." This reasoning is difficult to understand and not commensurate with the requirements of the rule. Applicants do not understand the grounds for the rejection; however, applicants will answer to the best of their understanding.

The rejection may not stand, because claims 89-91 are not directed to pharmaceutical compositions comprising particular polymorphic forms of ondansetron hydrochloride. The Office Action of July 28, 2004, rejected claims 89-91 as allegedly failing to comply with the enablement requirement. However, claims 89-91 are directed to pharmaceutical compositions comprising "ondansetron hydrochloride" of a particular size and not to polymorphic forms of ondansetron. Consequently, the rejection of claims 89-91 under 35 U.S.C. § 112, first paragraph as lacking enablement cannot stand and should be withdrawn.

Claims 45 and 66 were rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Office asserts that claims 45 and 66 are indefinite because they are "directed to the anhydrous ondansetron hydrochloride compound, but it contains water." Office Action dated July 28, 2004, p. 4. Applicants respectfully traverse.

"Determining whether a claim is definite requires an analysis of whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Solomon v. Kimberly-Clark Corp.* 216 F.3d 1372, 55 U.S.P.Q.2d 1279 (Fed. Cir. 2000) citing *Personalized Media Communications, LLC v. ITC*, 161 F.3d 696, 705, 48 U.S.P.Q.2d 1180, 1888 (Fed. Cir. 1998) (emphasis added). "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *Id.* In other words, the

definiteness of the claim language must be analyzed, not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art. *Solomon v. Kimberly-Clark Corp.* 216 F.3d 1372, 55 U.S.P.Q.2d 1279 (Fed. Cir. 2000) citing *In re Moore*, 439 F.2d 1232, 169 U.S.P.Q. 236 (C.C.P.A. 1971). When the specification states the meaning that a term in the claim is intended to have, the claim is examined using that meaning, in order to achieve a complete exploration of the applicant's invention and its relation to the prior art. *In re Zletz*, 893 F.2d 319, 13 U.S.P.Q.2d 1320 (Fed. Cir. 1989); M.P.E.P. 2173.05(a).

As to claim 45, the specification states: "Ondansetron hydrochloride Form B anhydrous of the present invention absorbs up to 2% moisture when exposed to 60% relative humidity. The water absorbed by the crystal is not within the crystal structure of a hydrous form as a hydrate water." Specification, p. 9, ll. 1-4. The specification, therefore, gives a precise definition to the language of claim 45, *i.e.*, an anhydrous ondansetron hydrochloride form B with about 2% water absorbed outside of the crystal structure. As such, one skilled in the art would understand the bounds of claim 45 when reading it in light of the definition given in the specification.

As to claim 66, the claim recites "ondansetron hydrochloride Form E", which is not described in the specification as being anhydrous. The specification states: "Ondansetron hydrochloride Form E contains 1.8%-2.0% water, as measured by Karl Fisher. This is a stoichiometric value corresponding to 1/3 molecule of water per molecule of ondansetron hydrochloride." Specification, p. 12, ll. 13-16. The specification further states: "[O]ndansetron hydrochloride Form E when exposed up to 60% relative humidity for one week can contain water up to 10%...." Specification, p. 12, l. 30 – p. 13, l. 2. The description of ondansetron hydrochloride Form E in claim 66 as containing water does not render the claim indefinite because the specification describes Form E as a hydrate.

Claims 10 and 16 were also rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Office asserts that the term "containing" in claims 10 and 16 is "vague and indefinite," because it "would imply that there are additional components besides the 5-10% water." Office Action dated April 20, 2005, p. 3. Applicants respectfully traverse.

To avoid any confusion, applicants have amended claims 10 and 16 to include the language recited in the specification, each claim now states "having." Thus, when the skilled artisan construes the claim term "having" in light of the disclosure of the specification, it is not indefinite. The specification states: "Ondansetron hydrochloride having a water content between 6% and 9%, intermediate between the monohydrate (5.18%) and dihydrate (9.85%) is reproducibly obtained by following the procedures of Examples 20-25." Specification, p. 7, ll. 26-28. The specification does not disclose additional components of the compound and, therefore, one skilled in the art, when reading claim 66 in light of the specification, would recognize that the term "having" is directed to the term of water content and not other additional components.

In view of the preceding amendments and arguments, the rejections of claims 10, 16, 45, and 66 under 35 U.S.C. § 112, second paragraph as indefinite cannot stand and should be withdrawn.

Claims 19-22, 49-50, 52, 57-58, 66-67, and 74-76 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wu Gousheng et al., CN 1113234 ("Gousheng"). Applicants respectfully traverse.

To anticipate a claim, a single reference must disclose the claimed invention with sufficient clarity to prove its existence in the prior art, and must disclose each and every element of the challenged claim. *Motorola Inc. v. Interdigital Technology Corp.*, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997); *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996). Absence from the reference of any claimed element negates anticipation. *Kloster Speedsteel AB v. Crucible Inc.*, 231 USPQ 160 (Fed. Cir. 1986). Furthermore, "[t]he identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 U.S.P.Q.2d 1913, 1920 (Fed. Cir. 1989).

Claims 19-22 are directed to anhydrous ondansetron hydrochloride and anhydrous ondansetron hydrochloride Form B having a particular PXRD pattern, respectively. Claims 49-50 are directed to ondansetron hydrochloride Form C having a particular PXRD pattern. Claim 52 is directed to ondansetron hydrochloride Form D having a particular PXRD pattern. Claims 57-58 and 66 are directed to ondansetron hydrochloride Form E having a particular PXRD pattern. Claim 67 is

directed to ondansetron hydrochloride Form E and H having a particular PXRD pattern. Claims 74-76 are directed to ondansetron hydrochloride Form I having a particular PXRD pattern.

Guosheng discloses ondansetron hydrochloride hydrates by way of generic Formula (I) and ondansetron free base Formula (II). *See* Gousheng, p. 1. Gousheng discloses the synthesis of ondansetron hydrochloride monohydrate and dihydrate in Embodiments A_1, A_2, and B. *Id.* pp. 8, 10, and 11. Even when dried under the desiccant P_2O_5, the dihydrate only yields the monohydrate. *Id.* Embodiment A_2 at p. 10. The synthesis of the free base form of ondansetron is disclosed in Embodiments C, D, E, and F. *Id.* at pp. 11-13.

The Guosheng reference does not anticipate claims 21-22, 49-50, 52, 57-58, 67, and 74-76, because the reference fails to teach each and every element of the claims. For example, the PXRD data is not disclosed for any of the ondansetron hydrochloride compounds in Gousheng. PXRD data is an element of each of claims 21-22, 49-50, 52, 57-58, 67, and 74-76. Since Gousheng does not disclose that element, it cannot anticipate these claims. Moreover, the Gousheng reference does not enable a skilled artisan to make the ondansetron hydrochloride recited in the claims.

The Office Action asserts that the claimed compounds are inherent in the disclosures of Guosheng; and, therefore, that the absence of PXRD data in Gousheng is of no consequence. *See* Office Action dated April 20, 2005, pp. 6-7. A prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991). Inherent anticipation does not require recognition of the missing characteristic in the prior art by a person of ordinary skill in the art. *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003).

In this case, Applicants have repeated the procedures recited in Embodiments A_1, A_2, and B of Gousheng and have obtained ondansetron hydrochloride monohydrate and dihydrate described in Gousheng. *See* 37 C.F.R. 1.132 Declaration of Revital Lifshitz dated June 24, 2003, ¶¶ 6-10. Applicants have also analyzed those products by PXRD. *See* 37 C.F.R. 1.132 Declaration of Judith Aronhime dated June

24, 2003, ¶¶ 6-10. Table 1 below summarizes the PXRD peaks found for the ondansetron hydrochloride monohydrate and dihydrate disclosed in Gousheng, and compares them to the PXRD peaks found for the ondansetron hydrochloride forms claimed in the present application.

Table 1: Comparison of PXRD Data for Compounds Disclosed in Gousheng to Compounds Claimed by Applicants.

Compounds in Gousheng		Compounds Claimed by Applicants					
Monohydrate	Dihydrate	B	C	D	E	H	I
6.1	6.1		6.3		6.3		
							6.9
					7.4		
						7.8	
				8.3			8.2
							8.7
			9.2				9.1
							9.3
							9.9
			10.2				
		10.5			10.5		
					11.2		11.1
							11.6
		11.9					
12.4	12.4				12.3		
		13.0	13.1		13.0		
		13.5					
				14.0		14.0	13.8
					14.5		
				14.8		14.8	
		15.1					
					15.9		16.1
17.0	17.0		16.9		17.0		16.9
							17.9
18.3	18.3						
19.2	19.2						
20.3	20.3				20.1		
20.9	20.9	20.9			20.8		
							21.1
		22.7					22.7
23.3	23.3						
24.1	24.1	24.0					
			24.4		24.5	24.7	
				25.5			25.0
25.8	25.8	25.7				25.6	25.7
					26.2		
							26.6
					27.2		27.4
28.1	28.1						27.9
30.3	30.3						

* This Table has been created from PXRD data described in the Specification for ondansetron hydrochloride monohydrate, dihydrate, and Forms B, C, D, E, H, and I (*See* Specification, p. 3, ll. 17-20, p. 6, ll. 5-9, p. 8, ll. 25-28, p. 11, ll. 13-15, p. 12, ll. 10-12, p. 13, ll. 18-20, p. 14, ll. 4-6), as well as PXRD data described in the Declaration of Judith Aronhime (*See* 37 C.F.R. 1.132 Declaration of Judith Aronhime dated June 24, 2003, Appendix A and B).

Table 1 illustrates that each of the forms of ondansetron hydrochloride of claims 21-22, 49-50, 52, 57-58, 66-67, and 74-76 has a PXRD pattern different from those of the compounds disclosed in Gousheng. Gousheng, therefore, cannot inherently disclose the claimed PXRD patterns. Since each claimed form contains PXRD peaks that are not expressly or inherently disclosed in Gousheng, Gousheng does not meet each and every element of the claims.

Moreover, the Office has stated "Applicants can overcome the 102(b) rejection, by showing that their anhydrous crystalline form and polymorphs of Ondansetron is different from the prior [art]." Office Action dated April 20, 2005, p. 7. Table 1 shows that Applicants have done so.

The Guosheng reference fails to anticipate claims 19-20 and 66, because the reference does not teach an ondansetron hydrochloride anhydrate. As discussed above, the Guosheng reference discloses ondansetron hydrochloride dihydrate, which upon drying yields the monohydrate. The Guosheng reference also teaches the free base ondansetron without water (it is unclear whether the compound is an anhydrate). The hydrochloride salt is never disclosed. Failing to disclose the chloride, the Guosheng reference also fails to disclose the anhydrate ondansetron hydrochloride.

Additionally, the Guosheng reference does not enable the skilled artisan to make the anhydrate ondansetron hydrochloride. While disclosing how to make ondansetron hydrochloride dihydrate and monohydrate, even when the reference dries the dihydrate, at best, it can only synthesize the monohydrate. Thus, the Guosheng reference cannot teach how to make the anhydrate compound.

In light of the foregoing, the rejection of claims 19-22, 49-50, 52, 57-58, 66-67, and 74-76 under 35 U.S.C. § 102(b) as anticipated by the Guosheng reference cannot stand and should be withdrawn.

Claims 5-8, 10-22, 25-39, 41, 43, 45-70, and 72-91 were rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of the Guosheng reference.

The Federal Circuit in *In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999), set forth three requirements to make out a *prima facie* case of obviousness under 35 U.S.C. § 103(a) in light of the prior art. In order to be *prima facie* obvious: (i) there must be some teaching or suggestion in the prior art to modify a reference to form the claimed invention, (ii) there must be a reasonable expectation of success taught or suggested in the prior art, and (iii) all of the elements of the claimed invention must be found in the prior art. *See also* M.P.E.P. § 2143. In order to meet its burden to show that the claims are *prima facie* obvious in light of the prior art, the Office must expressly point to something in the reference itself, something in the nature of the problem to be solved, or something in the general knowledge of persons reasonably skilled in the art that would constitute objective evidence of a teaching or suggestion to modify the reference to obtain the claimed invention. *See In re Sang Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002).

The Examiner can satisfy the burden of showing obviousness of the combination only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. *In re Sang Su Lee*, 277 F.3d 1338, 1343, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002); citing *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed. Cir. 1992). The need for specificity is paramount, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. *Id.* The Examiner's conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority. *Id.*

Claims 5-8, 10-18, 25-38, 46-48, 51, 53-56, 59-61, 68-70, and 77-86 are directed to processes of preparation of various forms of ondansetron hydrochloride.

The Guosheng reference discloses three processes for preparing ondansetron hydrochloride dihydrate and monohydrate. *See*, Gousheng, Embodiments A_1, A_2, and B at pp. 8, 10, and 11. Embodiment A_1 discloses a process for preparing ondansetron hydrochloride dihydrate encompassing the steps of mixing ondansetron free base with ethyl acetate, heating the mixture, eluting the product through a silica column with ethyl acetate, 1N HCl, and water in succession, concentrating the aqueous solution

collected, and cooling to crystallize ondansetron hydrochloride dihydrate. *Id.* at p. 8. The crystals of ondansetron hydrochloride dihydrate were converted into the monohydrate form by drying in the presence of P_2O_5. *Id.* Embodiment A_2 recites a process for preparing ondansetron hydrochloride dihydrate encompassing the steps of mixing ondansetron free base with ethanol, agitating the mixture, collecting the resulting resin, rinsing the resin with ethanol, drying the resin, adding 0.1 N HCl to the resin, agitating the mixture, rinsing the resin with portions of 0.1 HCl and collecting the filtered acid portions, combining the filtered acid portions, concentrating, and cooling to crystallize ondansetron hydrochloride dihydrate. *See* Gousheng, description p. 10. The crystals of ondansetron hydrochloride dihydrate were converted into the monohydrate form by drying in the presence of P_2O_5. *Id.* Embodiment B recites a process for preparing ondansetron hydrochloride dihydrate encompassing the steps of recrystallizing ondansetron free base from methanol, drying the free base, dissolving the free base in ethanol, passing HCl gas through the solution to obtain a pH of 3, chilling the solution, and crystallizing ondansetron hydrochloride dihydrate. *See* Gousheng, description p. 11. the ondansetron hydrochloride dihydrate was then recrystallized from water. *Id.*

The Guosheng reference does not teach or suggest the procedure of claims 5-7 which encompass processes for converting ondansetron hydrochloride dihydrate to ondansetron hydrochloride monohydrate by contacting the dihydrate crystals with a water: ethanol mixture. As discussed above, the Guosheng reference discloses that drying ondansetron hydrochloride dihydrate in the presence of P_2O_5 yields only the monohydrate form. In at least two embodiments, the Guosheng reference dries the dihydrate to obtain the monohydrate only. In contrast, claims 5-7 recite a process where ondansetron hydrochloride dihydrate is mixed with a water and ethanol solution to yield the monohydrate. In contrast to the Guosheng reference, the conversion to the monohydrate uses water and not a drying agent such as P_2O_5. Accordingly, the Guosheng reference teaches against the present claims by adding a water removing agent instead of using a water-containing solution.

The Office Action concludes that "the prior art has offered that the use of water-alcohol solvent is possible in the preparation of ondansetron hydrochloride" and offers as proof Embodiment C_4 of the Guosheng reference. Applicants first observe that Embodiment C_4 yields ondansetron free base, not ondansetron hydrochloride.

The basis of the rejection is flawed, because it is the wrong compound. Also, it is n-propyl alcohol and 0.3 N HCl that are used as reaction solvents and not crystallization solvents. The reaction mixture was worked up as described in Embodiment C_2 where it was chilled, the solids filtered, and recrystallized from methanol, not an ethanol-water mixture. Accordingly, not only is the rejection based upon the wrong compound, the rejection generalizes the role of a reaction solvent and a crystallization solvent without suggestion or motivation.

Claim 8 recites a procedure for converting ondansetron hydrochloride monohydrate to ondansetron hydrochloride dihydrate by exposing the monohydrate to an atmosphere of 50% humidity or greater. The Guosheng references does not disclose any process that utilizes a humid atmosphere to hydrate ondansetron hydrochloride. The reference makes the dihydrate from the starting materials and the addition of 0.1 N HCl. In fact, the Guosheng reference does not disclose any process for converting the monohydrate into the dihydrate. Since Gousheng is silent as to the limitations of claim 8, it cannot teach or suggest the process of claim 8. The Office asserts that the use of a humid atmosphere for hydration is suggested by Gousheng Embodiment C, where "the final product is rinsed with water in the preparation of Ondansetron hydrochloride." *See* Office Action dated April 20, 2005, p. 9. The embodiment cited by the Office Action, however, is directed to the synthesis of ondansetron free base and not ondansetron hydrochloride. *See* the Guosheng reference at p. 11. The water in Gousheng removes impurities, which is supported by the statement "rinsing with water during filtration." The water does not hydrate the ondansetron free base and there is no suggestion that water performs such action. As such, Embodiment C of Gousheng does not teach or suggest the process of claim 8. Moreover, as discussed above, the Guosheng reference dries the compound using P_2O_5, a commonly known drying agent, and this teaching is contrary to treating the compound to a humid atmosphere.

As to claim 8, the Office Action concludes that "concerning the use of the 50% relative humidity and making an intermediate degree of hydration, the prior art has offered guidance that the final product is rinsed with water in the preparation of Ondansetron hydrochloride (see page 11, Embodiment C); therefore, it is possible for the skilled artisan to adjust the exposure of water to the final product depending on the artisan' desirability of increasing water content in the final product." Applicants

note that Embodiment C is directed to ondansetron free base and not the hydrochloride. Once again, the Office Action premised the rejection on the wrong compound. Also, the standard is not whether "it would be possible," but whether "it is desirable" to alter the water content. The Office Action again states an "obvious to try" standard without formulating the suggestion or teaching informing the skilled artisan of the desirability to obtain the recited compound. Rinsing a compound with water to remove impurities is not a suggestion to expose a compound to humidity to increase water content. The Office Action does not explain how the skilled artisan would equate the two actions.

Claims 25-38 encompass processes of preparing anhydrous ondansetron hydrochloride by treating ondansetron hydrochloride with a dry alcohol or a dry organic solvent. Because the Guosheng reference does not teach or disclose the anhydrous form of ondansetron hydrochloride, the reference cannot disclose or suggest methods of preparing the same. As noted above, the only dehydrating method disclosed in the Guosheng reference dehydrates ondansetron hydrochloride dihydrate with the drying agent P_2O_5 to obtain the monohydrate. *See* Guosheng at p. 8, 10. This disclosure does not teach or suggest the complete dehydration of the dihydrate or monohydrate much less dehydration by treatment with a dry alcohol or dry organic solvent as recited in claims 25-38.

Claims 46-48 encompass processes of preparing anhydrous ondansetron hydrochloride Form B by reacting HCl gas with a toluene solution of ondansetron free base. As previously noted, Gousheng does not teach the anhydrous form of ondansetron hydrochloride, or methods of preparing an anhydrous hydrochloride form. Nevertheless, the Office Action asserts that Applicants' use of toluene is obvious in light of Gousheng's use of benzene in Embodiment D_1 because of toluene's "similar functionality" to benzene. *See* Office Action dated April 20, 2005, p.10. The benzene in Gousheng's Embodiment D_1, however, is used in the synthesis of ondansetron free base to extract the product from the aqueous reaction mixture (1000 ml of ice water was previously added), and not to crystallize or prepare ondansetron hydrochloride. *See* Guosheng at p. 12. The Office's comparison, therefore, is inapposite.

To properly perform the obviousness analysis, toluene must be compared to the solvents disclosed by Gousheng for the preparation of ondansetron hydrochloride.

Gousheng discloses ethanol, ethyl acetate, and water in the preparation of ondansetron hydrochloride dihydrate. *See* Guosheng at p. 8, 10, 11. Toluene does not have similar functionality to these solvents. Ethanol, ethyl acetate, and water are polar, hydrophilic solvents, while toluene is non-polar and hydrophobic. Moreover, Applicants recite toluene to prepare anhydrous ondansetron hydrochloride, in contrast the Guosheng reference uses ethanol, ethyl acetate, and water to prepare ondansetron hydrochloride dihydrate. Benzene is merely a solvent used for the extraction of the product, which is removed by evaporation, and not a reaction solvent or a crystallization solvent. Therefore, the skilled artisan would not be motivated to substitute toluene for ethanol, ethyl acetate, or water based on the disclosure of Guosheng. Additionally, the skilled artisan would not be motivated to use the extraction solvent benzene for crystallization without the guidance of the present application.

Claims 53-56 encompass processes of preparing ondansetron hydrochloride polymorphic Form D by melting ondansetron hydrochloride in the presence of xylene and adding the melt to ethanol. As with claims 46-48, the Office Action asserts that Applicants' use of xylene is obvious in light of Gousheng's use of benzene in Embodiment D_1 because of xylene's "similar functionality" to benzene. *See* Office Action dated April 20, 2005, p.10. For the reasons discussed in the immediately preceding paragraphs, the Office's argument must fail. Xylene, like toluene, is non-polar and hydrophobic, while the solvents disclosed in Gousheng for the preparation of ondansetron hydrochloride dihydrate are polar and hydrophilic. Again, benzene is used as an extraction solvent and not a crystallization solvent. There is simply no suggestion to alter the role of benzene in the reaction. The Office Action allude to an obvious "use;" however, there is not motivation or teaching for such an alteration. In fact, two changes must take place to meet the argument by the Office Action. First, the skilled artisan must change xylene for benzene. Second, the skilled artisan must change the role of benzene from an extraction solvent to a crystallization solvent. However, neither teaching or suggestion is present in the Guosheng reference, much less any reasonable expectation that such changes would result in a novel ondansetron hydrochloride Form D. Thus, the Guosheng reference does not teach or suggest the use of xylene in the preparation of ondansetron hydrochloride dihydrate.

Claims 59-61 encompass processes of preparing ondansetron hydrochloride polymorphic Form E by treating ondansetron hydrochloride in isopropanol. The Office asserts that it would have been obvious to use isopropanol in preparing ondansetron hydrochloride dihydrate in light of Gousheng's use of n-propanol in Embodiment C_2. *See* Office Action dated April 20, 2005, p. 10. The n-propanol in Gousheng's Embodiment C_2, however, is used as a reaction solvent in the synthesis of ondansetron free base, and not in the preparation of ondansetron hydrochloride. *See* Guosheng at p. 11. The Office's comparison, therefore, is inapposite. To properly perform the obviousness analysis, isopropanol must be compared to the solvents disclosed by Gousheng for the preparation of ondansetron hydrochloride. Gousheng discloses ethanol, ethyl acetate, and water in the preparation of ondansetron hydrochloride dihydrate. The Guosheng reference does not suggest isopropanol as a solvent, does not suggest isopropanol as a crystallization solvent, and does not suggest that ondansetron hydrochloride as a novel polymorphic Form E will be formed.

Claims 77-81 encompass processes of preparing ondansetron hydrochloride polymorphic Form I by exposing ondansetron hydrochloride to methanol vapor. The Guosheng reference does not disclose any process of preparing ondansetron hydrochloride involving exposure to vapor or even to methanol. Methanol is disclosed in Gousheng as a solvent for recrystallizing ondansetron free base. *See* Gousheng, p. 11 (Embodiments B and C_2). Since Gousheng is silent as to the limitations of claims 77-81, it cannot teach or suggest the process of claims 77-81.

Claim 10-18 and 51 encompass processes of preparing ondansetron hydrochloride using ethanol, ethanol/isopropanol, chloroform, toluene, and/or ethanol/toluene solvents for crystallization. Chloroform, toluene, and isopropanol are not disclosed by Gousheng in the crystallization of ondansetron hydrochloride. Claims 68-70 encompass processes of preparing ondansetron hydrochloride using ether as a crystallization solvent. Ether is not disclosed by Gousheng in the crystallization of ondansetron hydrochloride. Claims 82-86 encompasses processes of preparing anhydrous ondansetron hydrochloride. Gousheng does not disclose or suggest the anhydrous form of ondansetron hydrochloride, or any procedures for its preparation. Therefore, the disclosures of Gousheng cannot render claims 10-18, 51, 68-70, and 82-86 obvious.

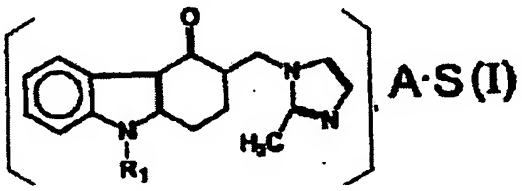
The Office Action proposes that "the limitation of a process with respect to ranges of pH, time and concentration does not impart patentability to a process when such values are those which would be determined by one of ordinary skill in the art achieving optimum operation of the process." None of claims 10-18 and 51 recite a range of pH, time, or concentration. Thus, optimization of these ranges is irrelevant to the obviousness analysis of the claims. Furthermore, generalizations such as "well understood by those of ordinary skill in the art to be a result-effective variable" is mere conjecture without substantiation.

The mere statement that "concerning the use of making polymorphs and the use of various solvent, it is not uncommon to find several polymorphs of compounds existing under normal handling conditions" is merely the basis for an "obvious to try" argument based upon unsupported conjecture. The statement lacks the specificity needed to make particular findings as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed. In this case, like that of *In re San Su Lee*, the conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority.

In light of the foregoing arguments, the rejection of process claims 5-8, 10-18, 25-38, 46-48, 51, 53-56, 59-61, 68-70, and 77-86 under 35 U.S.C. § 103(a) as obvious over Gousheng cannot stand and should be withdrawn.

Claims 19-22, 39, 41, 43, 45, 49-50, 52, 57-58, 62-67, 72-76, and 87-91 are directed to ondansetron hydrochloride compounds.

The Office asserts that these compounds are obvious in view of Gousheng's disclosure of ondansetron hydrochloride compounds of the general formula (I). *See* Gousheng, description p. 1. Formula (I) is depicted as follows:



A·S (I)

where A= hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, organic acids and inorganic acids; S = water; and $R_1 = C_1$-C_6 straight chains or alicyclic alkyls. *Id.*

Claims 19, 62-65, and 72-73 encompass ondansetron hydrochloride polymorphic forms with different solvents than those disclosed in Gousheng. Claim 19 encompasses anhydrous ondansetron hydrochloride, with no solvent molecules incorporated into the crystal structure. Claims 62-65 encompass ondansetron hydrochloride isopropanolate and claims 72-73 encompass ondansetron hydrochloride methanolate.

The Guosheng reference discloses hydrated ondansetron hydrochloride in Formula (I), and expressly limits the possible solvent incorporated into the crystal structure to water. *Id.* Therefore, Gousheng does not teach or suggest the anhydrous form or other solvated forms such as those having isopropanol or methanol. If the Guosheng teaches anything, it is that various acids (item (A)) and organic groups (R_1) can be varied to obtain different compounds. The solvent (S) is never varied, nor is the solvent completely removed. At best, the Guosheng reference yields a monohydrate when removing water from the dihydrate under drying conditions (P_2O_5).

Claims 39, 41, 43, 87, and 88 encompass ondansetron hydrochloride polymorphic forms having specific particle sizes. In addition to failing to suggest any polymorphic form, the Guosheng reference does not disclose or suggest particle size at all. The disclosed methods for synthesizing ondansetron hydrochloride dihydrate also fail to yield the polymorphs recited in the claims. Thus, not only is the skilled artisan left with no teaching as to the variables, such as solvent, necessary to achieve the recited polymorphs, the skilled artisan is never suggested any particle size. Consequently, the Guosheng reference cannot teach or suggest specific particle sizes of the recited ondansetron hydrochloride. Simply, a reference cannot teach or suggest a feature that it does not disclose.

Claims 45, 49-50, 52, 57-58, 74-76, and 89-91 encompass ondansetron hydrochloride polymorphic forms B, C, D, E, H, I, and pharmaceutical compositions thereof. Gousheng does not teach or suggest any of these polymorphs, or any processes for preparing them. The Office maintains that since many compounds are known to exhibit polymorphism, the claimed polymorphic forms of ondansetron

hydrochloride are rendered obvious by Gousheng's disclosure of the compounds ondansetron hydrochloride monohydrate and dihydrate. *Prima facie* obviousness, however, requires that the prior art teach a "reasonable expectation of success."

Again, the Office Action sets forth a conclusory statement without substantiation and merely offers an "obvious to try" argument. Applicants reiterate what the Federal Circuit has repeatedly stated: "The statement lacks the specificity needed to make particular findings as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected the components for combination in the manner claimed." As discussed before, in this case, like that of *In re San Su Lee*, the conclusory statements do not adequately address the issue of motivation to combine; the factual question of motivation is material to patentability, and can not be resolved on subjective belief and unknown authority.

Polymorphism and polymorph generation are considered to be unpredictable by those skilled in the art: "[T]he possibility of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious." Joel Bernstein, *Polymorphism in Molecular Crystals* 9 (Clarendon Press 2002). "No rules exist that allow prediction of whether a compound will exhibit polymorphism;" Byrn, S.R. *Solid-State Chemistry of Drugs* p. 7 (Academic Press 1982). "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found. Brittian, H.G., *Polymorphism in Pharmaceutical Solids* p. 185 (Marcel Dekker 1999).

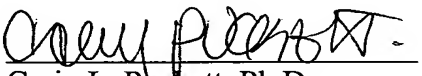
Since polymorphism is an unpredictable art, Gousheng's mere disclosure of ondansetron hydrochloride, with no discussion or indication of polymorphic behavior, could not lead one skilled in the art to believe that he would be reasonably successful in finding or preparing the claimed polymorphic forms of ondansetron hydrochloride. At most it might be obvious to try to find polymorphs of ondansetron hydrochloride from the disclosures of Gousheng, but "obvious to try" is not the legal standard for establishing a *prima facie* case of obviousness. *See, e.g., In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). The Office, therefore, has not met its burden in making out a *prima facie* case of obviousness with respect to the claimed polymorphs.

Accordingly, the rejection of product claims 19-22, 39, 41, 43, 45, 49-50, 52, 57-58, 62-67, 72-76, and 87-91 under 35 U.S.C. § 103(a) as obvious over Gousheng cannot stand and should be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully submit that the present application is in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. No fee is believed to be due for the submission of this response. Should any fees be required, please charge such fees to Kenyon & Kenyon, LLP Deposit Account No. 11-0600.

Respectfully Submitted,

Date: January 30, 2006



Craig L. Puckett, Ph.D.
Reg. No. 43,023

KENYON & KENYON LLP
One Broadway
New York, NY 10004
Direct Dial: 212-908-6034
Fax: 212-425-5288